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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WYETH PATENT LAW GROUP 5 GIRALDA FARMS MADISON, NJ 07940			TONGUE, LAKIA J	
			ART UNIT	PAPER NUMBER
			1645	

DATE MAILED: 03/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/796,925

Applicant(s)

LI ET AL.

Examiner

Lakia J Tongue

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 1-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 20 and 21 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-19, drawn to a vaccine composition, classified in class 424, subclass 241.1.
- II. Claims 20-21, drawn to a method of reducing the shedding of e. coli, classified in class 424, subclass 184.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the composition can be used for protein expression.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Barbara Renda on January 12, 2005 a provisional election was made with traverse to prosecute the invention of Group II, claims 20-21. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on January 10, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

2. The use of the trademark Emulsigen (page 5) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

3. Claim 21 is objected to because of the following informalities: The word "neomycion" should be spelled neomycin. In addition, the word "acidophilis" should be spelled acidophilus. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 20-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to teach how the claimed vaccine composition with or without a *Lactobacillus acidophilus* or neomycin medicated feed supplement will reduce the shedding of E. coli O157 in an animal. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to E. coli O157 infection or disease induction

The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing or reducing the shedding of E. coli O157. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CRFC1988). The Wands factors to be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

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invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Apply the above test to the facts of record, it is determined that 1) no relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with regard to reducing shedding of E. coli O157, 3) there are no working examples which suggest a method for reducing the shedding of E. coli O157 in an animal when administering a composition comprising an immunogenically active component selected from inactivated or killed whole or subunit E. coli O157:H7 or mixtures thereof; a metabolizable oil adjuvant, optional pharmaceutical carrier, *Lactobacillus acidophilus* or neomycin medicated feed supplement, 4) the relative skill in the art is recognized as high, and 5) the state of the art in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

The preparation of an inactivated, killed or subunit of E. coli O157:H7 is not disclosed. Did applicant(s) make a composition? Were chemicals used? Was it heat killed to inactivate the E. coli? How was the composition prepared? The working example does not clearly provide support for the claimed invention (A method of reducing shedding of E. coli O157 in an animal).

The results of example 2 are not understood. Example 2 states, "calves are randomly divided into groups of six animals each (page 10, line 27). The data begins with groups 5,6 and 7 each having a different number of calves. What happened to groups 1-4? Where are the six animals for each group? On page 11 there is a table of

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data, which includes the following headings: the vaccine group, calf #, 0 days post first vaccination and 14 days post third vaccination. Group 5 has specifically pointed out 5 calves. There is a space below the 5th calf that only provides information for 0 days post first vaccination and 14 days post third vaccination. What do those numbers (group 5: 640 and 735; group 6: 735 and 868 and group 7: 573 and 1184) represent? There is no vaccine group or calf # present. This is true for groups 6 and 7 as well. There is to be six animals in each group. Why are there five animals in group 5, four animals in group 6 and three animals in group 7? Group 5 uses the unvaccinated control group. If the animals are unvaccinated at 0 days post first vaccination how do all five calves have a titer of 640? It is the same situation for the calves at 14 days post third vaccination, if the calves of group 5 are unvaccinated controls how does the titer of calf # 282 increase from 640 to 1280? Group 6 was the group that was given the conventionally adjuvanted vaccine. What is a conventionally adjuvanted vaccine? Calf # 389 and 277 both start and end with titers of 640. Calf # 292 starts with a titer of 2560 and ends with a titer of 2560 where is the enhanced response? The written information on page 11 does not reflect the data. Where is the *Lactobacillus acidophilus* or neomycin medicated feed supplement? The chart on page 12 is unclear. What is a dpv2? What are the units of measurement? Is applicant measuring immediate hypersensitivity? The examiner is unclear what is to be ascertained from this chart. How does the data from page 12 relate to shedding of *E. coli*?

The parameters of example 3 and the field of study are unclear. Example 3 is not in the provisional application and does not enable the claimed invention. Example 3

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discusses the effectiveness of various interventions (page 13, line 4), what were the various interventions? Example 3 state that "the vaccine stimulates the host immune system, specifically for both T cells and B cells to elicit humoral antibody and some CM1 factors" (page 13, line 9), where is the data for this information? Example 3 states that hide and fecal samples were collected (page 13, line 10). What are hide samples? The examples states "following collection....analyses were reported as percentages of hide fecal and hide or fecal samples testing positive for the pathogen, divided by the total samples collected per pen" (page 13, lines 11-14), where are the analyses that were reported? Example 3 states that the differences were determined using a chi-squared goodness of fit test (page 13, lines 17-18), where is the chi-square analyses? The example states that " the vaccine was found to reduce pathogen prevalence by 20.3% on hide samples and by 31.1% in fecal samples" (page 13, line 18-20), what were the controls? What was the experiment? Lastly, example 3 states that " the vaccine provides additional reduction in antigen shedding (page 13, lines 21-22), how much additional reduction? Where is the appropriate data for this?

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

For the benefit of priority, the specification of provisional application 60/454,182 does not fully support the claimed subject matter, thus the examiner is granting the filing date (3/10/04) of the instant application for art rejections.

5. Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Finlay et al (U.S. Patent Application Publication 2002/0160020 A1).

Claim 20 is drawn to a method for reducing shedding of *E. coli* O157 in an animal which comprises the treatment of the animal with the composition which comprises an immunogenically active component selected from the group consisting of inactivated or killed whole or subunit *E. coli* O157:H7, or mixtures thereof; a metabolizable oil adjuvant; and optionally a pharmaceutically acceptable carrier.

Finlay et al discloses compositions and methods for stimulating an immune response against *Escherichia coli* (EHEC). Finlay et al provide a vaccination schedule effective to reduce EHEC shedding by a ruminant (0024), as well as a method for reducing shedding of EHEC (0039). In certain embodiments, the EHEC is EHEC O157:H7. Finlay et al disclose a method comprising administering to the mammal a therapeutically effective amount of a composition comprising EHEC O157:H7. In addition the mammal is a human or a ruminant, such as a bovine subject. The composition further comprises an immunological adjuvant, such as an oil-in-water emulsion which comprises e.g., a mineral oil (0036). The composition and method of Finlay is the same as the claimed composition and method. Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Finlay et al (U.S. Patent Publication 2002/0160020 A1) as applied to claim 20 above, and further in view of Brashears, M. et al (Isolation, selection, and Characterization of Lactic Acid Bacteria for a Competitive Exclusion Product To Reduce Shedding of *Escherichia coli* O157:H7 in Cattle, *Journal of Food Protection*, 2003; 66(3): 355-363).

Claim 21 is drawn to a method for reducing shedding of *E. coli* O157 in an animal which comprises the treatment of the animal with the composition which comprises an immunogenically active component selected from the group consisting of inactivated or killed whole or subunit *E. coli* O157:H7, or mixtures thereof; a metabolizable oil adjuvant; and optionally a pharmaceutically acceptable carrier.

Finlay et al teaches compositions and methods for stimulating an immune response against *Escherichia coli* (EHEC). Finlay et al provides a vaccination schedule effective to reduce EHEC shedding by a ruminant (0024), as well as a method for reducing shedding of EHEC (0039). Finlay et al teach a method comprising administering to the mammal a therapeutically effective amount of a composition comprising EHEC O157:H7. In addition the mammal is a human or a ruminant, such as

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a bovine subject. The composition further comprises an immunological adjuvant, such as an oil-in-water emulsion which comprises e.g., a mineral oil (0036). The reference differs because it does not teach the limitation of a *Lactobacillus acidophilus*.

Brashears et al teaches that lactic acid bacteria were selected on the basis of characteristics indicating that the bacteria would be good candidates for a competitive exclusion product that would reduce the shedding of *Escherichia coli* O157:H7.

Lactobacillus acidophilus among others were the most commonly identified lactic acid bacteria (title and abstract, page 355)

Finlay et al and Brashears et al are analogous in that they teach inventions related to reducing the shedding of *E. coli* O157 in an animal. As such it would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to modify Finlay et al with Brashears et al. It would have been expected, barring evidence to the contrary, that adding probiotics would be effective in reducing the shedding of *E. coli* O157 in an animal.

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Zhao, T. et al (Reduction of Carriage of Enterohemorrhagic *Escherichia coli* O157:H7 in Cattle by Inoculation with Probiotic Bacteria, Journal of Clinical Microbiology, 1998; 641-647) because it teaches the administering a probiotic followed by *E. coli* O157:H7 to reduce the level of carriage in most animals.


Cray, W. et al (Effect of Dietary Stress on Fecal Shedding of *Escherichia coli* O157:H7 in calves, Applied and Environmental Microbiology, 1998; 1975-1979) because it teaches that E. coli was administered to reduce the fecal shedding of *Escherichia coli* O157:H7 in calves.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakia J Tongue whose telephone number is 571-272-2921. The examiner can normally be reached on Monday-Friday 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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